Remarks

Claims 1-40 are pending and under consideration. The Examiner has withdrawn claims 6, 7, 12, 19-36, 39 and 40 from further consideration in the subject application. Applicants have hereinabove amended claim 1. Support for the amendment to claim 1 may be found, inter alia, in the specification at page 18, lines 6-9. Applicants maintain that none of the changes to the claims raises an issue of new matter. Therefore, entry of this Amendment is respectfully requested.

Claim Rejections Under 35 U.S.C. §102

Stein et al.

The Examiner rejected claims 1-5, 13-15, 17 and 18 under 35 U.S.C. §102(b) as allegedly anticipated by Stein et al. (1999). The Examiner stated that these claims are drawn to a composition comprising a peptide moiety covalently bound to an antibody wherein the peptide comprises a poly-L-arginine peptide having a nitrogen-containing side chain comprising a guanido group and wherein the peptide moiety has various ranges of length.

The Examiner asserted that Stein et al. teaches a complex of an antibody conjugated to an HIV Tat (37-72) peptide. The Examiner also asserted that since HIV Tat (37-72) is replete with Lys, Arg and $(Arg)_3$ residues and the structures of Lys and Arg contain nitrogen and guanido groups, the reference teaches an arginine-rich peptide covalently linked to an antibody, meeting the limitation of "a peptide moiety comprising an amino acid residue having a nitrogen-containing side chain" as recited in claim 1, the limitation of "wherein the nitrogen-containing side chain comprises a guanido group" as recited in claim 2, the "poly-L-

arginine" as recited in claims 3-5, and the limitations of a monoclonal antibody and polyclonal antibody as recited in claims 17 and 18. The Examiner stated that the HIV Tat (37-72) peptide of Stein et al. is 36 amino acids long, which reads on the limitation of "at least 10 amino acid residues in length" as recited in claim 13; the limitation of "between about 10 amino acid residues and about 100 amino acid residues" as recited in claim 14; and the limitation of "between about 25 amino acid residues and about 75 amino acid residues" as recited in claim 15.

In response, applicants respectfully traverse the Examiner's rejection. Briefly, amended claim 1 provides a composition of matter comprising an antibody and a peptide moiety wherein the peptide is covalently bound to a carbohydrate moiety on a CH2 domain of the antibody.

Stein et al. teach conjugates of anti-tetanus $F(ab')_2$ fragments and a fragment of the HIV Tat protein. However, this reference does not teach a composition of matter comprising an antibody and a peptide moiety wherein the peptide is covalently bound to a carbohydrate moiety on a CH2 domain of the antibody. Applicants note that the CH2 domains of an antibody are located in the F_c portion of the antibody, not the $F(ab)_2$ portions (see Exhibit A). Stein et al. therefore do not teach a composition of matter comprising an antibody and a peptide moiety wherein the peptide is covalently bound to a carbohydrate moiety on a CH2 domain of the antibody, and thus fail to teach each and every element of the rejected claims.

Frankel et al.

The Examiner rejected claims 1-5, 8-11, 13-18 and 37 under 35

U.S.C. §102(e) as allegedly anticipated by Frankel et al. (U.S. Patent No. 6,316,003). The Examiner stated that the subject claims are drawn to the above mentioned composition with further limitations of molecular weight, 13 kD, within the range between 11 kD and 16 kD, and of being combined with a pharmaceutically acceptable carrier in a pharmaceutical composition.

The Examiner asserted that Frankel et al. teaches the use of transport peptides to deliver cargo molecules, particularly, an antibody, meeting the limitation of a monoclonal antibody and polyclonal antibody as recited in claims 17 and 18, respectively. The Examiner also asserted that the reference discloses transport peptides such as portions of HIV Tat protein (see column 3, lines 21-31, and SEQ ID NOs: 1-7, for example), meeting the limitations of "a peptide moiety comprising an amino acid residue having a nitrogen-containing side chain" as recited in claim 1, "wherein the nitrogen-containing side chain comprises a guanido group" as recited in claim 2, the "poly-L-arginine" as recited in claims 3-5, the molecular weight recited in claims 8 and 9, and the various lengths recited in claims 10, 11, and 13-16. The Examiner stated that the reference also teaches pharmaceutical, prophylactic and diagnostic compositions comprising transport polypeptide-cargo conjugates (citing column 3, lines 13-20; column 10, lines 66-67; column 11, lines 1-19), which are embodied by the terms "pharmaceutical carrier" recited in claim 37.

In response, applicants respectfully traverse the Examiner's rejection. Again, amended claim 1 provides a composition of matter comprising an antibody and a peptide moiety wherein the peptide is covalently bound to a carbohydrate moiety on a CH2 domain of the antibody.

Frankel et al. teach a conjugate comprising an antibody and an HIV Tat fragment made by a different method than the method described in the subject specification. Frankel et al. describe reacting an antibody with excess sulfo-SMCC and then adding the HIV Tat fragment, whereas the subject specification describes reacting an antibody with sodium periodate and then linking the peptide via Schiff base formation. Frankel et al. do not teach whether the reaction described therein causes the HIV Tat fragment to bind to a carbohydrate moiety on the CH2 domain of the antibody or some other domain of the antibody. Therefore, Frankel et al. do not teach, either explicitly or inherently, a composition of matter comprising an antibody and a peptide moiety wherein the peptide is covalently bound to a carbohydrate moiety on a CH2 domain of the antibody, and thus fail to teach each and every element of the rejected claims.

Rothbard et al.

The Examiner rejected claims 1-5, 8-11, 13-16, 37 and 38 under 35 U.S.C. §102(e) as allegedly anticipated by Rothbard et al. (U.S. Patent No. 6,306,993). The Examiner stated that these claims are drawn to the above mentioned composition in a kit.

The Examiner asserted that Rothbard et al. teaches compositions of transport-enhancing polymers containing guanidino side chains (citing abstract, particularly, column 2, lines 45-67), specifically, poly-arginine polypeptides (column 3, lines 16-25), covalently attached to a biologically active agent for enhanced transport (citing abstract and columns 9-10), which reads on the limitations of claims 1-5 and 37. The Examiner also asserted that the reference teaches that the use of naturally occurring L-amino acid residues in the transport polymers has

the advantage that breakdown products should be relatively non-toxic to the cell or organism (column 8, lines 26-34). The Examiner stated that the reference further discloses sequences of transport peptides consisting of 4, 5, 6, 7, 8, 9, 15, 20, 25 and 30 L-arginine polymers, and a mixture of longer L-arginine polymers of up to 100 amino acids, with an average molecular weight of 12,000 Daltons (column 12, lines 1-9; columns 31-34), which reads on the different molecular weights and peptide lengths as recited in claims 8-11 and 13-16. The Examiner stated that the reference discloses that the composition may additionally be packaged with instructions for using it (column 4, lines 36-38), which reads on "a kit comprising the composition of claim 1 and instructions for use" as recited in claim 38.

In response, applicants respectfully traverse the Examiner's rejection. Again, newly amended claim 1 provides a composition of matter comprising an antibody and a peptide moiety wherein the peptide is covalently bound to a carbohydrate moiety on a CH2 domain of the antibody.

Rothbard et al. teach attachment of transport molecules to single-chain variable region fragments of antibodies (scFv). However, this reference does <u>not</u> teach a composition of matter comprising an antibody and a peptide moiety wherein the peptide is covalently bound to a carbohydrate moiety on a CH2 domain of the antibody. Applicants note that variable region fragments (scFv) of antibodies are distinct from the constant region fragments (CH2) described by applicants (see Exhibit A). Rothbard et al. therefore do not teach a composition of matter comprising an antibody and a peptide moiety wherein the peptide is covalently bound to a carbohydrate moiety on a CH2 domain of the

antibody, and thus fail to teach each and every element of the rejected claims.

In view of the above remarks, applicants maintain that claim 1, and claims 2-5, 8-11, 13-18, 37 and 38 which depend therefrom, satisfy the requirements of 35 U.S.C. §102(a). Therefore applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Claim Rejections Under 35 U.S.C. §103

The Examiner rejected claims 1-5, 8-11, 13-18, 37 and 38 under 35 U.S.C. §103(a) as allegedly unpatentable over Futaki et al. (February, 2001) in view of Awwad et al. (1994).

The Examiner stated that as mentioned above, these claims are directed to a composition comprising an antibody covalently bound to a peptide moiety, specifically, a poly-L-arginine peptide.

The Examiner asserted that Futaki et al. describes delivery of exogenous proteins into cells using various arginine-rich peptides conjugated to carbonic anhydrase. The Examiner also asserted that the reference discusses the translocation activity of peptides of 4-16 arginine residues and states that eight residues, or an "octa-peptide" as recited in claim 11, would be an optimal number for efficient translocation. The Examiner stated that the reference further discusses the chemical conjugation of carbonic anhydrase to poly-arginine peptides.

The Examiner further stated that Futaki et al. does not teach the delivery of antibody by covalent linkage to poly-L-arginine

peptides, or the peptide moiety of 68 amino acids in length.

The Examiner asserted that Awwad et al. describes the modification of antibody carbohydrates by conjugation, which corresponds to a covalent bond between a peptide and an antibody.

The Examiner also asserted that it would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the cargo protein covalently linked to arginine-rich peptide from carbonic anhydrase of Futaki et al. to an antibody, as suggested by Awwad et al. The Examiner further asserted that the person of ordinary skill in the art would have been motivated to make that modification because it improves cellular uptake of an antibody and one would have expected success because Awwad et al. points out that modification of antibody by conjugation does not interfere with antibody effector functions.

The Examiner asserted that furthermore, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to increase the length of the peptide to 68 amino acids as routine optimization, thus resulting in the practice of the instantly claimed invention with a reasonable expectation of success.

In response to the Examiner's rejection, applicants respectfully traverse, and maintain that the Examiner has failed to establish a prima facie case of obviousness against the rejected claims.

Again, amended claim 1 provides a composition of matter comprising an antibody and a peptide moiety wherein the peptide

is covalently bound to a carbohydrate moiety on a CH2 domain of the antibody.

To establish a prima facie case of obviousness, the Examiner must demonstrate three things with respect to each claim. First, the cited references, when combined, teach or suggest each element of the claim. Second, one of ordinary skill would have been motivated to combine the teachings of the cited references at the time of the invention. And third, there would have been a reasonable expectation that the claimed invention would succeed.

Futaki et al. teach intracellular delivery of an enzyme, carbonic anhydrase, which was covalently conjugated with arginine rich peptides of varying lengths. However, this reference does not suggest using an antibody having a peptide covalently bound to a carbohydrate moiety on a CH2 domain of the antibody. Nowhere is it suggested that such a method could be used for the intracellular delivery of an antibody.

Awwad et al. disclose site-specific attachment of metal chelators or cytotoxic agents to the carbohydrate moiety of an antibody. Nowhere is it suggested that such attachment could be used to attach an arginine-rich peptide to an antibody.

To support a case of prima facie obviousness, Futaki et al., and Awwad et al., when combined, would have to teach or suggest all elements of the rejected claims. Moreover, there would have to have been a motive to combine them, and a reasonable expectation of the invention's success at the time of the invention. Again, one element of each rejected claim is the covalent attachment of a peptide to a carbohydrate moiety on a CH2 domain of the antibody. Thus, at the very least, these references, when

combined, would have to teach or suggest this element.

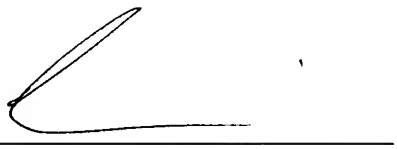
This they fail to do. In addition, and consequently, there is simply no motivation or suggestion to combine the references to create the instant invention. The collection of cited references is the result of the Examiner's impermissible use of hindsight to combine these references based on knowledge of applicants' specification. Devoid of any support to the contrary, an "invitation to try," which applicants do not concede exists, is considered inadequate support for an obviousness rejection.

Accordingly, the Examiner has failed to establish the prima facie obviousness of claims 1-5, 8-11, 13-18, 37 and 38 over these references. For the same reasons, applicants alternatively maintain that the rejected claims would not have been obvious over Futaki et al. and Awwad et al.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee is deemed necessary in connection with the filing of this Amendment. If any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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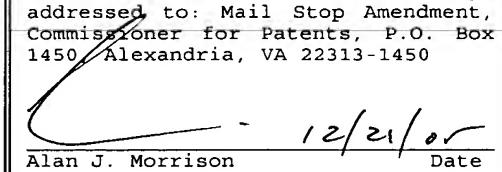

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Alan J. Morrison — Date
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